



iNOS promotes CD24⁺CD133⁺ liver cancer stem cell phenotype through a TACE/ADAM17-dependent Notch signaling pathway

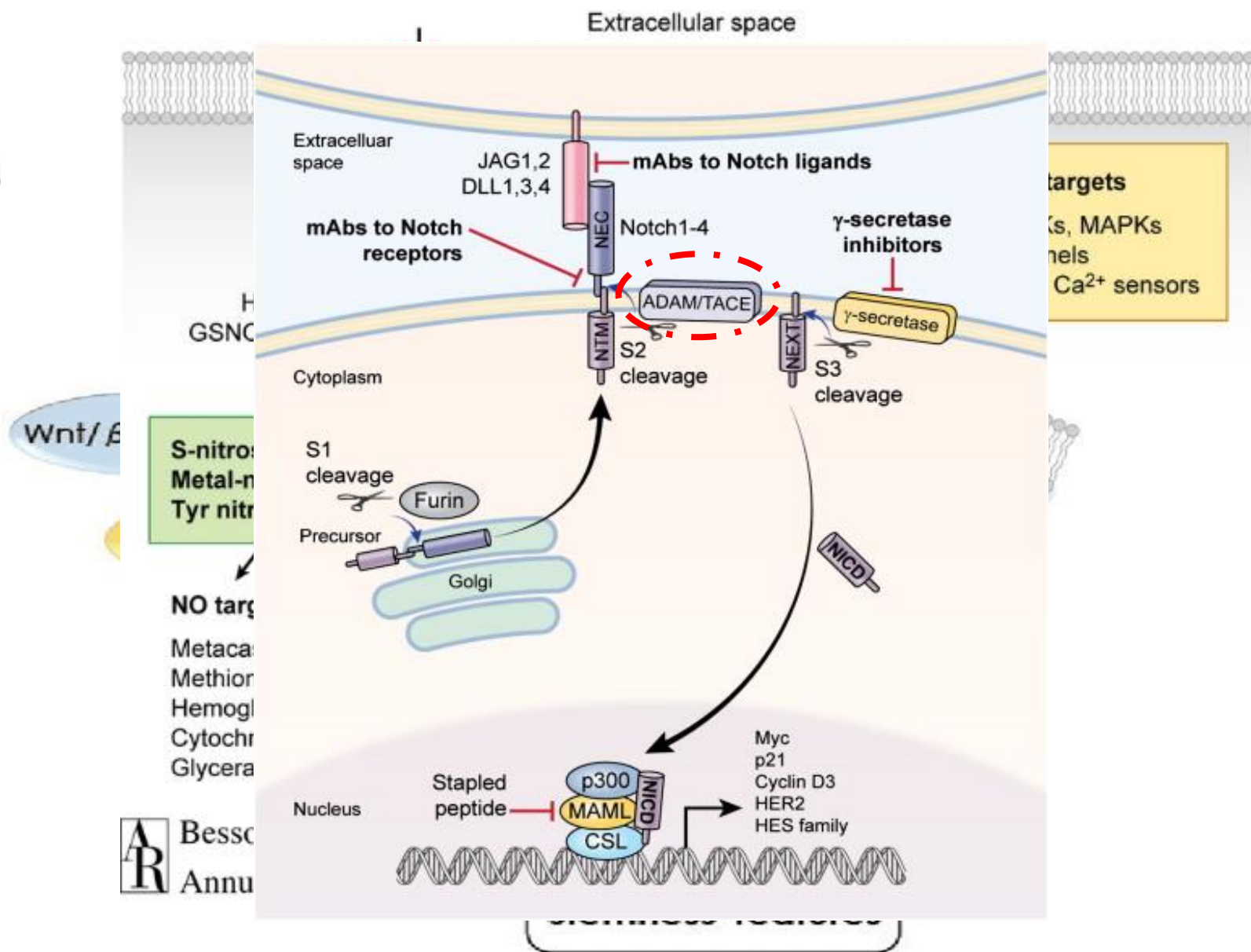
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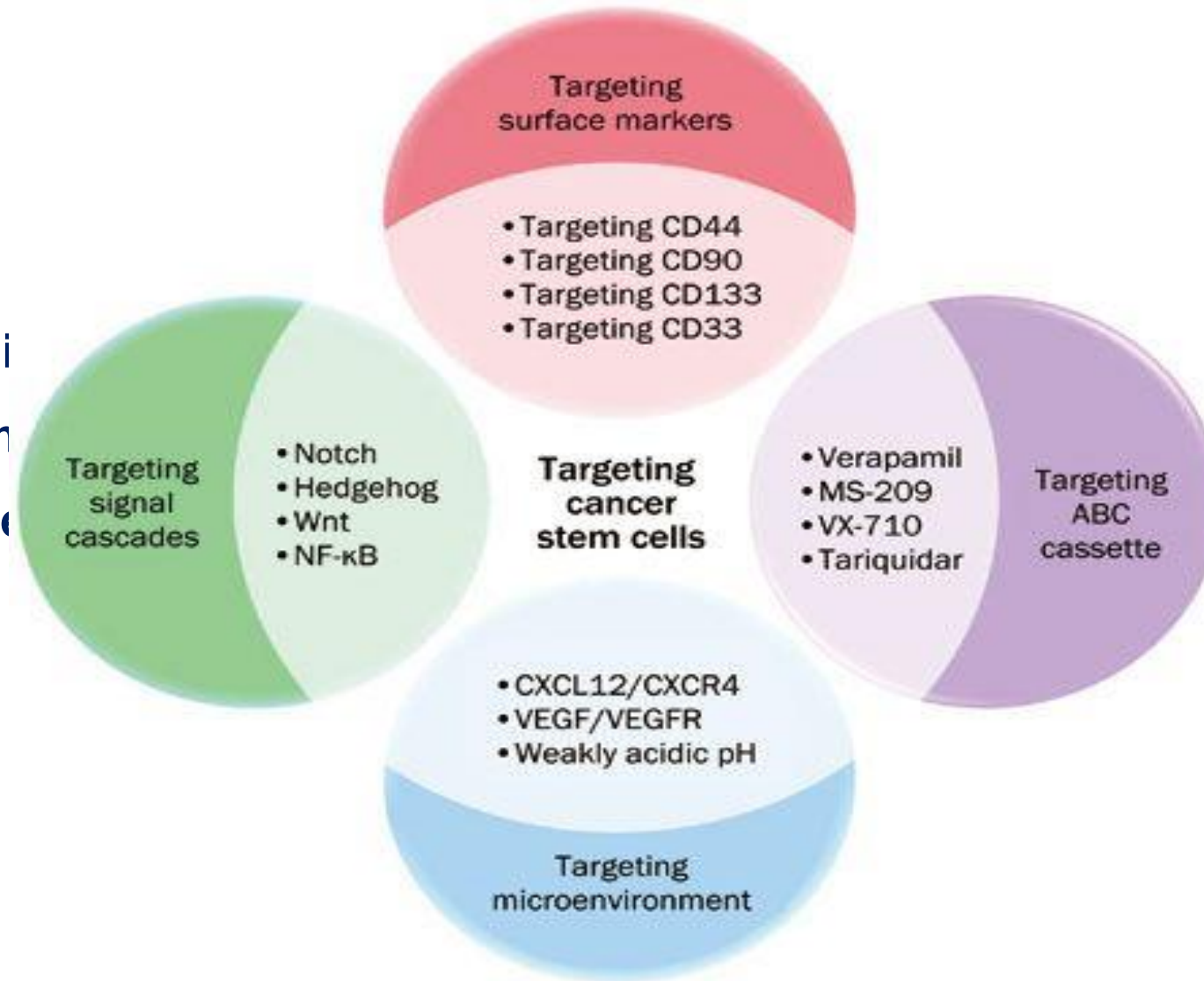
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Introduction



Therefore, it is activated in and treatment



pathways
diagnosis

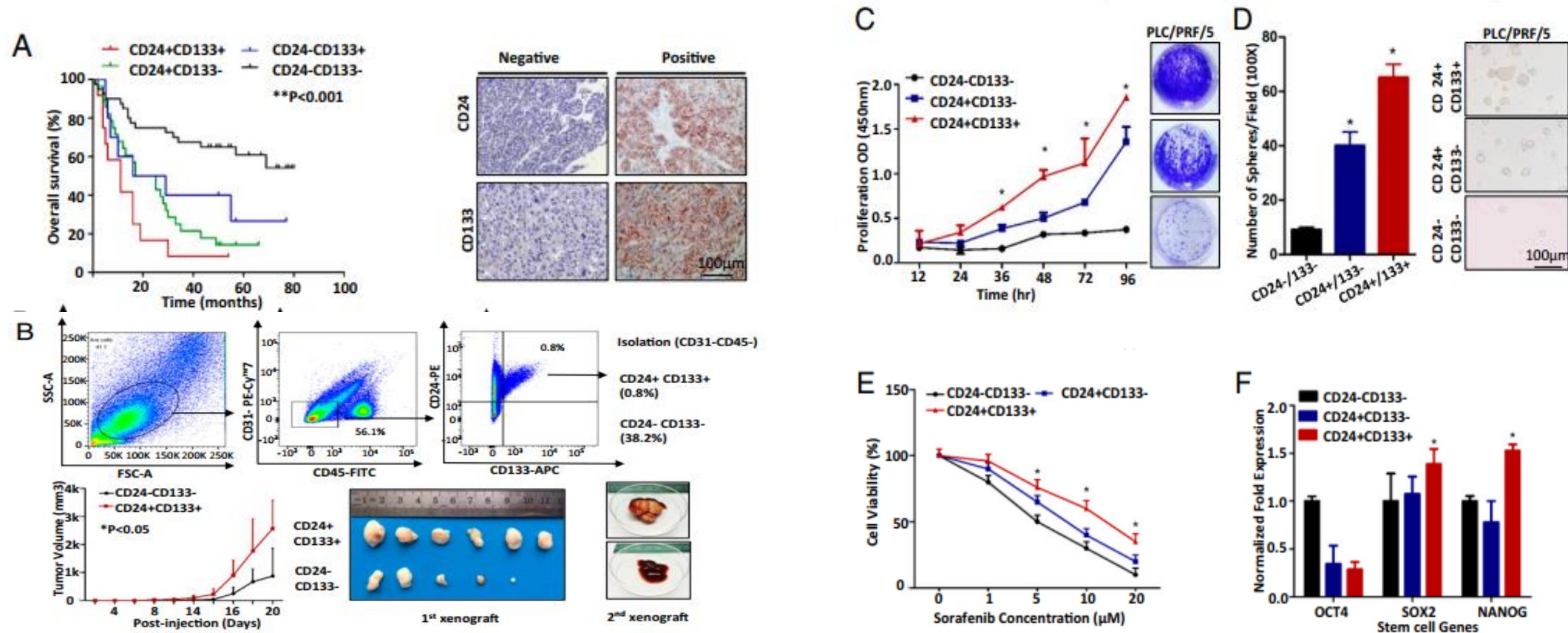
Hypothesis

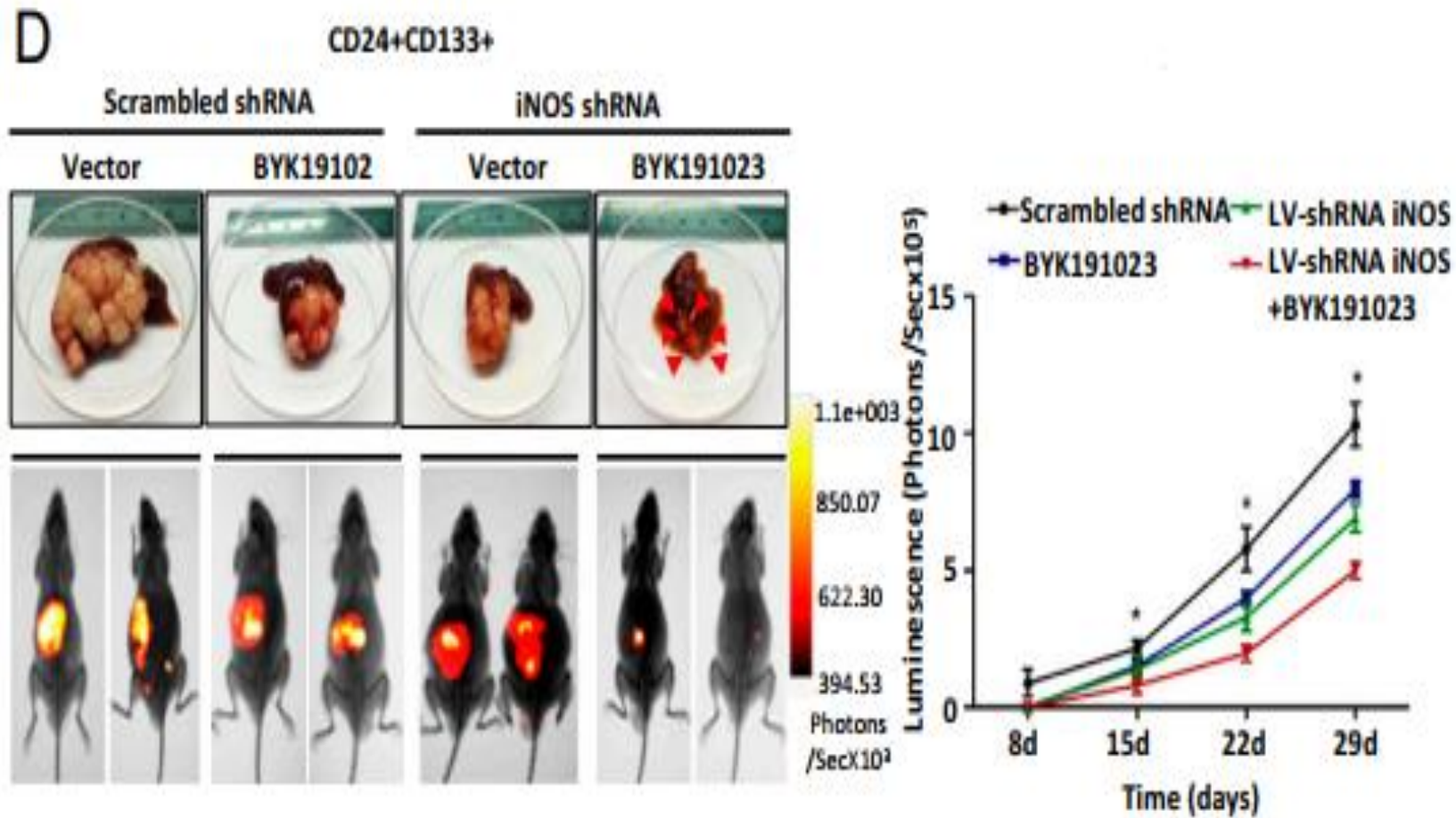
iNOS/NO promotes Notch1 activation through TACE/ADAM17 activation in liver cancer stem cells (LCSCs), leading to a more aggressive cancer phenotype.

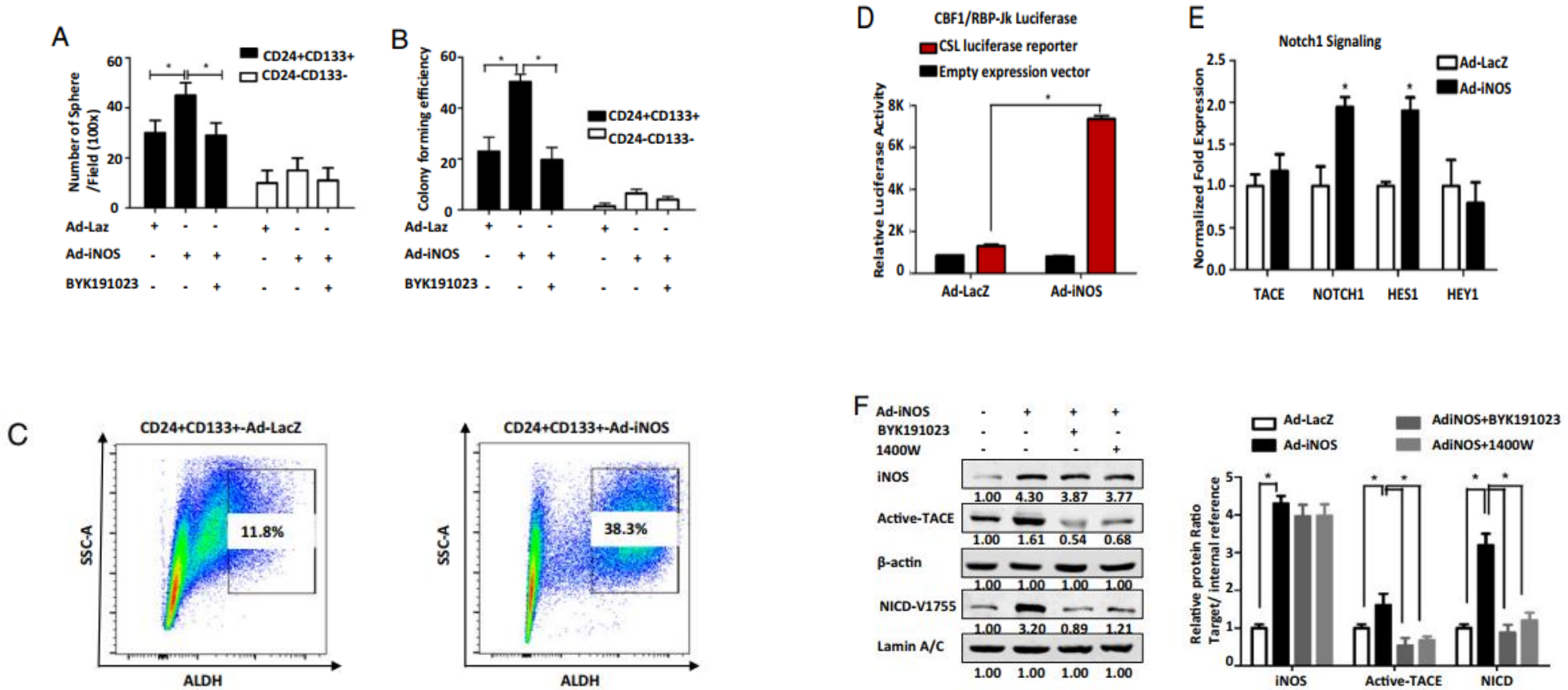
ADAM: A Disintegrin and Metalloprotease
TACE: TNF α -Converting Enzyme

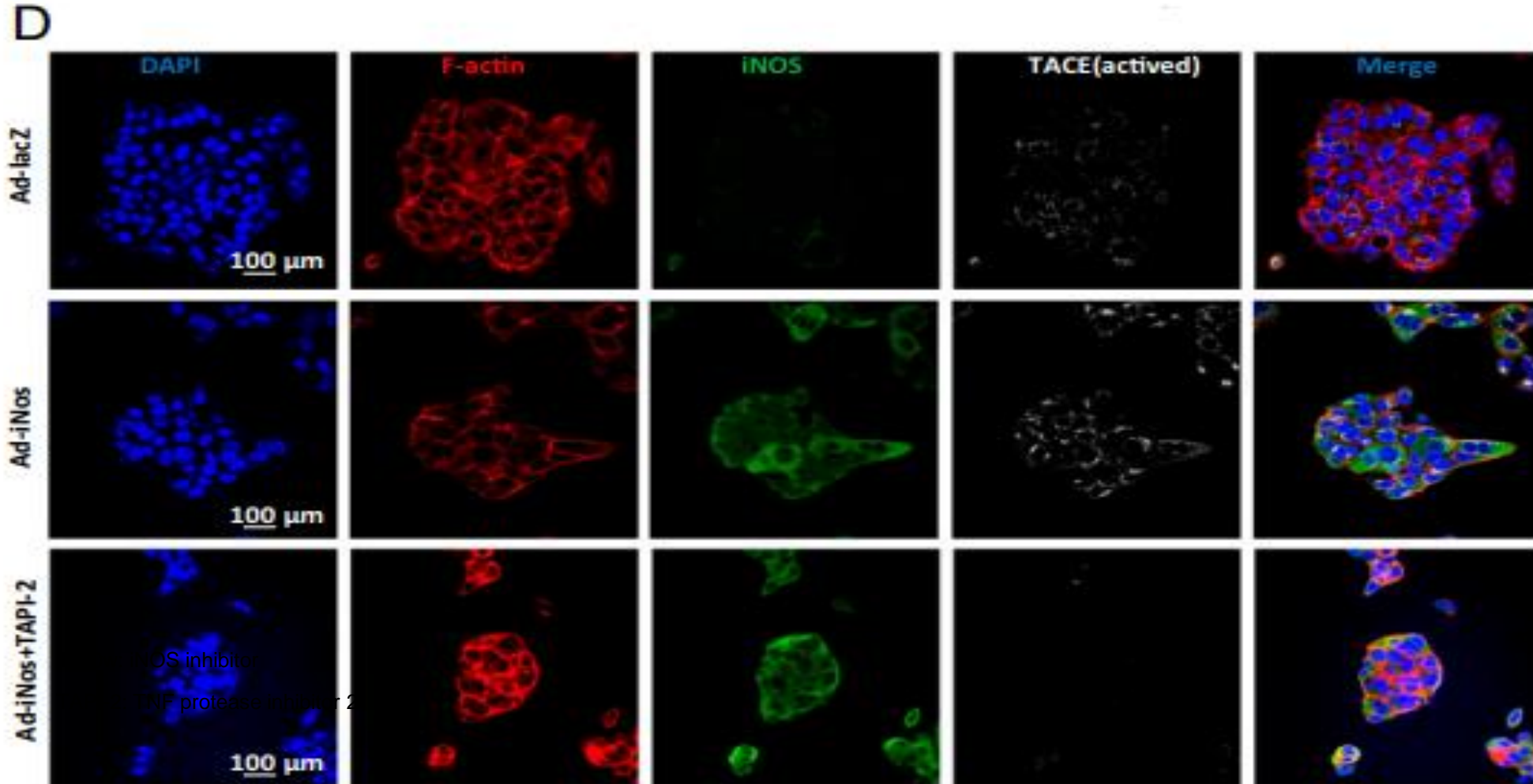
CD24+CD133+ HCC cells possess stem/progenitor cell characteristics.

CD133+CD24+ cells would contribute to the progression of HCC

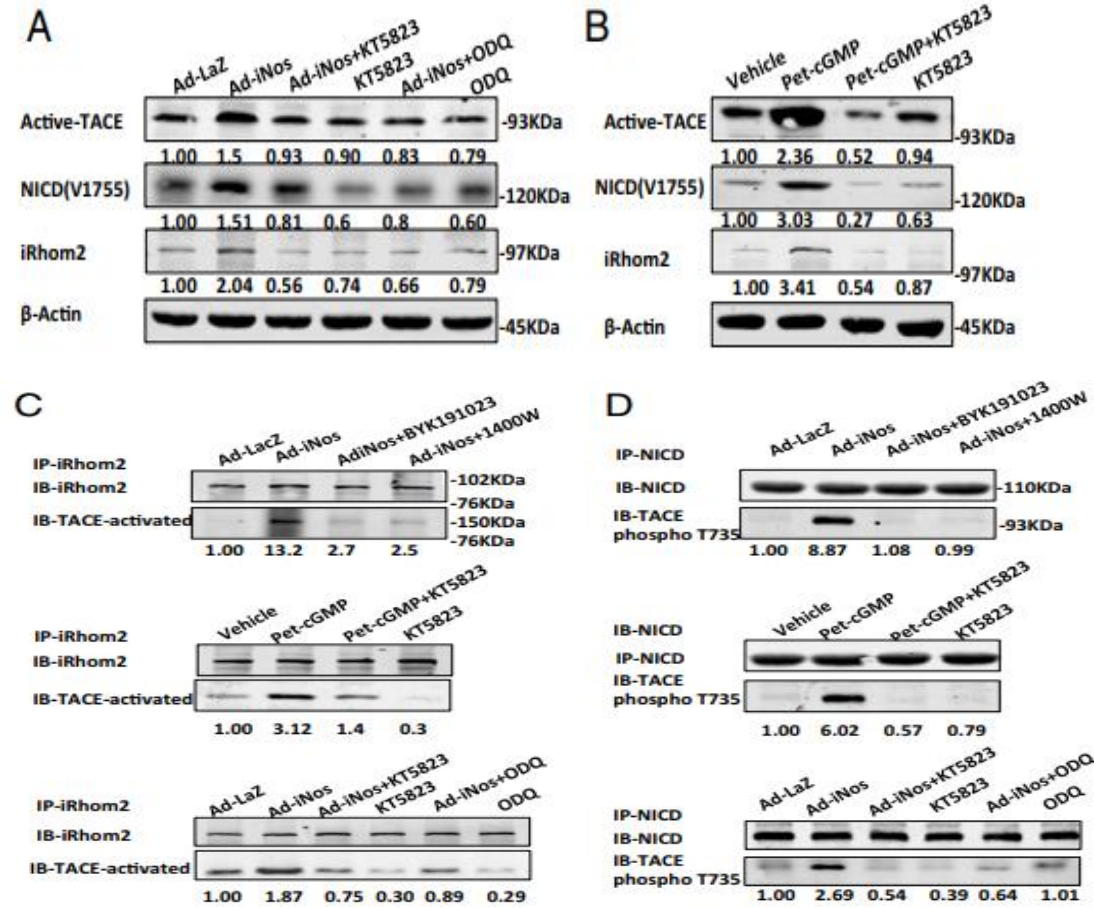








TACE Binds to iRhom2 and Activates Notch Signaling in LCSCs in an iNOS/cGMP/PKG-Dependent Manner



iRhom2: inactive rhomboid protein 2

ODQ : cGC inhibitor

KT5823 : PKG inhibitor

Br-PET-cGMP :A non-hydrolyzable cGMP analog and potent activator of PKG

Elevated iNOS Expression Is Associated with Poor Prognosis in Patients with HCC and Positively Correlated with TACE and Notch1 Levels.

A



F

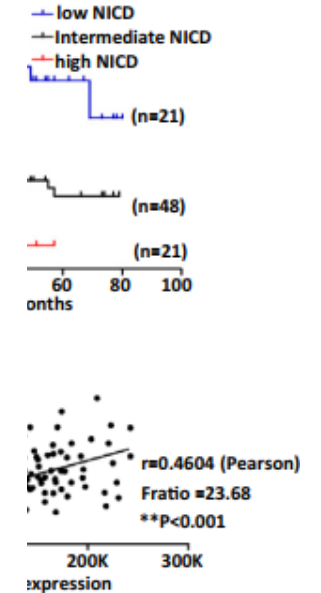
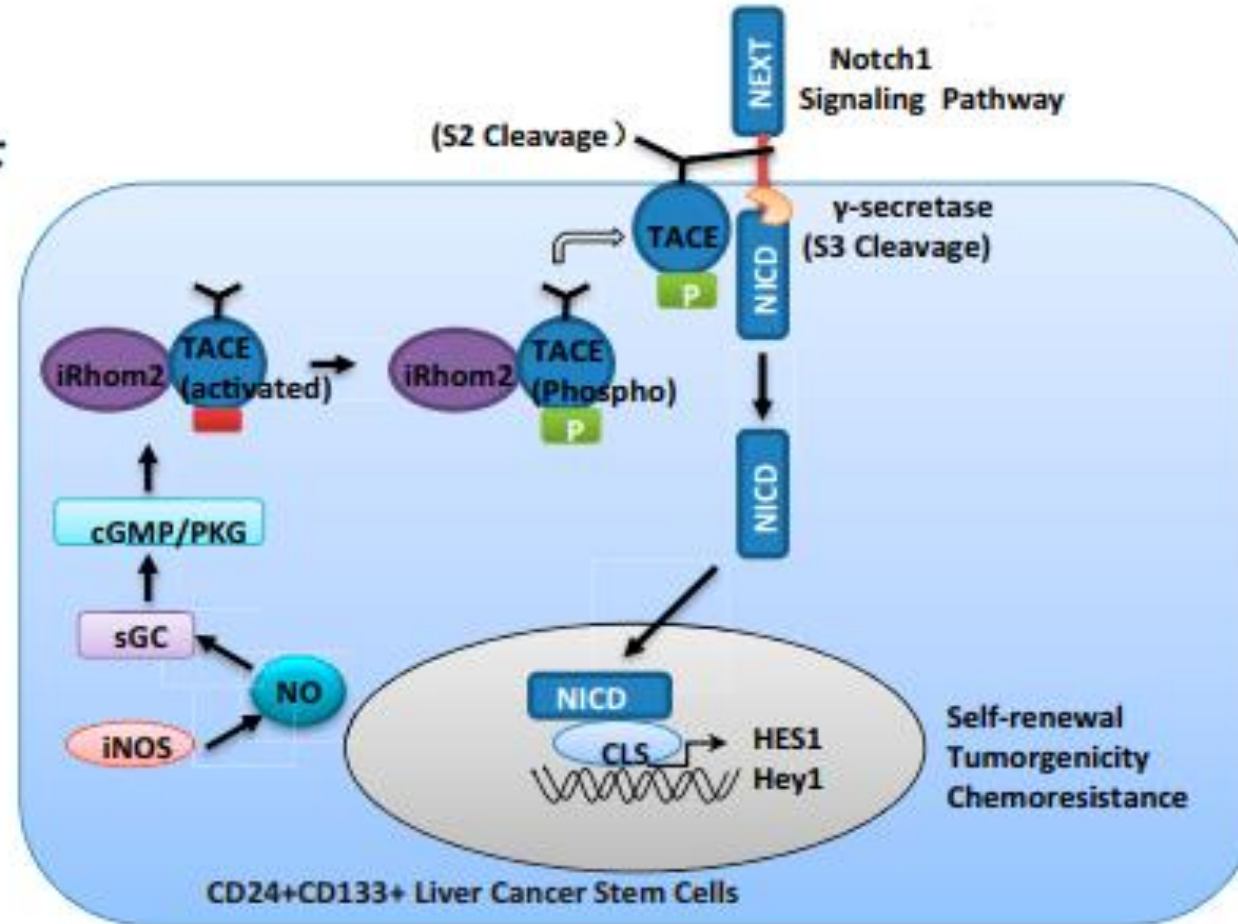


Table 1. Association of high NOS2 expression with tumor characteristics

Clinicopathological characteristic	iNOS (n = 90)		NICD (n = 90)	
	OR (95%CI)	P	OR (95%CI)	P
Gender (male/female)	3.5 (0.86–14.22)	0.079	2.96 (0.74–11.83)	0.125
Age, y (<60/≥60)	1.63 (0.62–4.31)	0.324	1.40 (0.53–3.69)	0.494
Grade (1/2/3 stage)	1.61 (0.59–4.38)	0.350	1.89 (0.69–5.17)	0.213
Microsatellites (absence/presence)	2.38 (0.52–10.9)	0.261	4.66 (1.08–21.93)	0.05*
Tumor size (<5 cm/≥5 cm)	1.38 (0.48–3.96)	0.550	0.54 (0.19–1.56)	0.256
Gross classification (massive/nodular/diffuse type)	0.78 (0.23–2.67)	0.686	0.66 (0.19–2.28)	0.513
Venous infiltration (absence/presence)	4.80 (1.22–18.65)	0.025*	14.24 (3.11–65.15)	0.0006**
TNM stage (low/high)	3.72 (1.11–12.52)	0.034*	3.37 (1.01–11.23)	0.048*
CD24 (low/high)	2.80 (1.70–4.62)	0.032*	2.53 (1.01–6.37)	0.049*
CD133 (low/high)	1.36 (1.57–3.23)	0.049*	2.55 (1.65–3.72)	0.033*

The IHC score of iNOS, TACE/Adam17, and activated Notch (NICD) in HCC was stratified into low, moderate, strong, and high for the analysis. "Low" is defined as expression less than onefold relative to mean values in normal tissue, whereas "high" is defined as expression greater than twofold relative to mean values in normal tissue. "Intermediate" expression is the range between low and high. Logistic regression was performed, with adjustments for age at diagnosis, gender, TNM stage, and neoadjuvant therapy. TNM stage was stratified into low (stage I/II) and high (stage III/IV). CD24 and CD133 counts were stratified into low (below the median) versus high (above the median).

* $P < 0.05$, ** $P < 0.01$; significant difference (logistic regression, χ^2 test). Numbers in boldface font indicate statistical difference.



